T-Cell Maturation

Introduction

T-cell maturation starts in the bone marrow, as all lymphocyte maturation does. But unlike B cells, prothymocytes leave the bone marrow very early in their development to mature in the thymus. This is why they're called T cells, because they mature in the thymus. There they go through a process of cell marker expression, positive selection, and negative selection. The result is one of two possibilities:

(1) a CD8 cytotoxic T cell (cytotoxic T lymphocyte; CTL) with a T-cell receptor (TCR) and CD3,
or
(2) a CD4 T-helper cell with a T-cell receptor (TCR) and CD3.

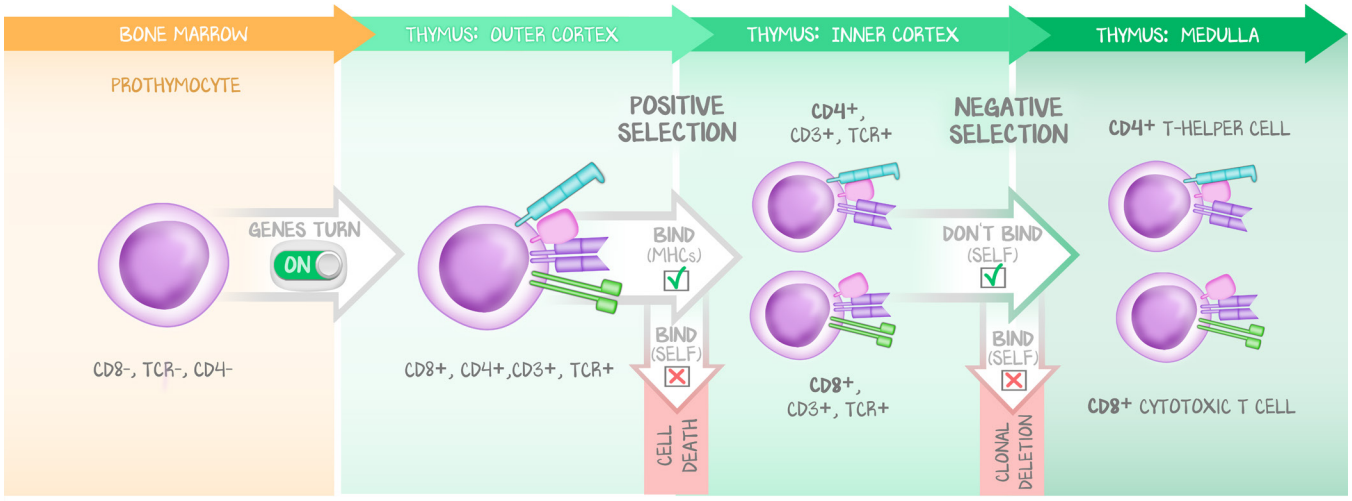

Figure 9.1: Progression of T-Cell Maturation
The prothymocyte arrives at the thymus naive and not expressing anything. In the outer cortex, the TCR, CD3, CD4, and CD8 turn on. In the inner cortex, positive selection ensures that the TCR works. Then the medulla ensures tolerance with negative selection. The output is either a CD8 CTL or a CD4 T helper.

The Things That Matter to T-Cell Maturation

CD markers can help you to more accurately identify "is this a T or a B cell?." T-cell CD markers are usually single digits and are always less than 20. The major players are:

CD3 (all T cells have this) which enables the TCR to function.

CD4 will recognize and bind to class 2 MHCs (**MHC-2**) and are destined to become CD4 T-helper cells (T_H).

CD8-positive cells that recognize class 1 MHCs (**MHC-1**) are destined to become cytotoxic T lymphocytes (CTL or Tc).

All T cells have a single genetically related molecule on the cell surface called the **T-cell receptor** (TCR). The TCR is rigid, is never lost, and is designed to bind **only** to **peptides complexed to an MHC**.

CD10 and TdT are both expressed in both B-cell lymphoblasts and T-cell lymphoblasts.

Bone Marrow

The bone marrow is a **primary lymphoid organ** dedicated to the maturation of lymphocytes. The bone marrow is only the first part of a T-cell's maturation to full functionality. **Immature and naive prothymocytes** leave the bone marrow without any of the things that make them T cells. They are essentially "naked." They won't have the TCR or the CD3, and are considered double-negative, expressing neither CD4 nor CD8.

Thymus Outer Cortex = Turning On

The same prothymocyte that left the bone marrow arrives in the thymus, the other **primary lymphoid organ**. It's **double-negative—**expressing neither CD4 nor CD8. It doesn't express a TCR. Nurse cells in the outer cortex of the thymus induce TCR expression in all cells that have CD3. Expressing a complete TCR is essential for the T cell to continue in the maturation process. At this time, though the mechanism remains unknown, the T cell becomes **double-positive,** expressing both **CD4** and **CD8**. At this point the T cell expresses TCR, CD3, CD4, and CD8. Expressing CD4 and CD8 is a requirement to move on to the next step, positive selection. Whether the T cell will eventually express only CD4 or only CD8 depends on whether the cell's TCR recognizes an MHC-1 (becomes a CD8 cell and loses its CD4) or an MHC-2 (becomes a CD4 cell and loses its CD8).

Thymus Inner Cortex = Positive Selection

The purpose of the T-cell receptor is to interact with MHC. Mature T cells that express CD8 will have a TCR that interacts with MHC-1. Mature T cells that express CD4 will have a TCR that interacts with MHC-2. In the outer cortex, the thymus made all of the T cells so that they were $CD4^+$ and $CD8^+$. The first question the thymus asks is, "can your TCR interact with an MHC at all?" The thymus shows the newly double-positive T cells antigens presented on both MHC-1 and MHC-2.

The inner cortex **doesn't use foreign antigen** for selection. The thymus has only self-antigen, so as you will see, it uses self-antigen to decide whether the T cell is able to do its job. This is done with two different types of selection, positive selection (this is first) and negative selection (this is second). We will start with positive selection. Positive selection rewards binding with life. It basically asks that new T cell to bind with any MHC it wants. If it can bind to an MHC, there is confirmation that the TCR on that T cell works, and that cell is allowed to further mature. If it can't bind to any MHC, then the TCR is broken, and that lineage needs to be stomped out. The cell dies through lack of signaling to keep it alive.

So to review the major points so far:

If the TCR binds to MHC-1, it's destined to become a CD8 cytotoxic T cell, and becomes $CD4^-$ $CD8^+$.

If the TCR binds to MHC-2, it's destined to become a CD4 T-helper cell, and becomes $CD4^+$ $CD8^-$.

If the TCR fails to bind either, it dies, and its cell line is removed.

Logically (not physiologically), what happens is that a TCR is there on the surface of a T cell. If the TCR-CD3 complex is intact and complete, it should function, which means it'll be able to bind MHC. Which MHC it binds to depends on what the costimulation is. A TCR-CD3-positive cell with both $CD4^+$ and $CD8^+$ has only one TCR. This means it can only bind one MHC at a time with its one TCR.

If the TCR-CD3-CD4-CD8 cell contacts an APC with MHC-2, the CD4 will stabilize, and CD8 disappears, leaving behind TCR-CD3-CD4. From then on, because it expresses CD4 and not CD8, it can only recognize MHC-2.

If the TCR-CD3-CD4-CD8 cell contacts an APC with MCH-1, then CD8 will stabilize, and the CD4 disappears, leaving a TCR-CD3-CD8 cell. From then on, because it expresses CD8 and not CD4, it can only recognize MHC-1.

If ANYTHING is broken, and the TCR-CD3-CD4-CD8 cell can't bind to an MHC . . . whether MHC-1 or MHC-2 . . . it means that the cell can't do its job. The thymus doesn't care why. It just says it's a defective cell line and eliminates it.

Positive selection **establishes that the TCR works** AND **establishes a phenotype** of a T cell. Said another way, positive selection means that if you bind, you live . . . AND if you bind, you get set to CD8 or CD4.

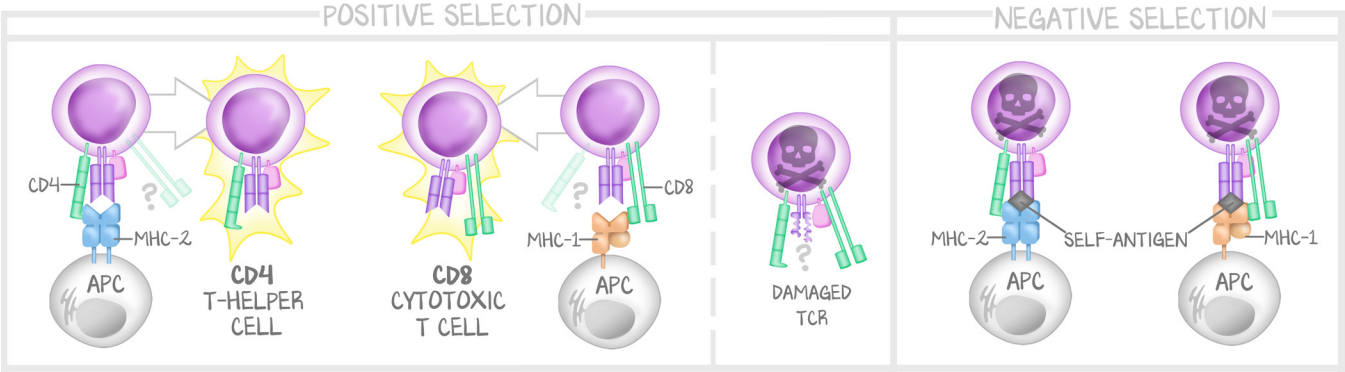

Figure 9.2: Positive and Negative Selection
Positive Selection. The only way a T cell would NOT bind the MHC-Ag complex is because the TCR itself is broken. Failure to bind results in death. In addition, the T cell can only bind one MHC-Ag at a time, either an MHC-1-Ag or an MHC-2-Ag, thereby stimulating the persistence of either CD4 or CD8. By exposing the now nearly mature T cell to self-antigens, the thymus assesses for tolerance. Binding here means that the T cell will recognize self as foreign, and must be deleted. Binding brings death. Clinically, lack of self-tolerance leads to autoimmunity. Negative selection, therefore, is a measure to reduce the risk of T cells that recognize and attack self.

Thymus Medulla = Negative Selection

Once in the medulla, all the T cells that interact correctly with the MHC are still alive. These T cells have also selected whether they'll express CD4 or CD8, depending on whether they recognized antigen presented on an MHC-1 APC or an MHC-2 APC. In order for APC-MHC-TCR to work, the T cell needs to have TCR, CD3, and either CD4 or CD8. At this point, all T cells have all the required pieces. They all can be activated. But now the final step is to ask whether the T cell knows the difference between self and non-self; that is, does it show **self-tolerance**.

They all CAN recognize foreign antigen-MHC, and therefore can be activated. We know that because of the positive selection process. However, we only want them to activate when they encounter *foreign* antigen. The thymus has only self-antigen to program T cells. In the inner cortex, we WANTED binding to self to ensure TCR worked. Now, in the medulla, we DON'T WANT the T cell binding to self with high affinity. The medulla **uses self-antigen** to assess for **self-tolerance**. Negative selection punishes a T cell with high-affinity binding to self with death. Binding to self with high-affinity means that T cell is willing to attack self and is a traitor. It needs to be eliminated.

How does the tolerance test occur? To test for tolerance, dendritic cells present self-antigens within their MHC complex. If a T cell either binds too tightly to the MHC–self-antigen complex (there are both MHC-2s for CD4 and MHC-1s for CD8) or identifies any self-antigen (the only thing APCs in the thymus are presenting) as non-self, it's programmed for death.

In summary, if you bind too tightly or do not recognize an antigen properly here, you die.

Positive selection gets rid of the defective ones. Negative selection gets rid of the overzealous.